UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,300	03/23/2001	Timothy W. Synold	1954-336	4635

6449 7590 01/13/2004

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
LAMBERTSON, DAVID A	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,300	SYNOLD ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of a reply to the previous Office Action, filed October 9, 2003. Amendments were made to the claims. Specifically, claims 1-67 were cancelled and new claims 68-78 were added.

Claims 68-78 are pending and under consideration in the instant application. Any rejection of record in the previous Office Action, mailed April 9, 2003, that is not addressed in this action has been withdrawn.

Because this Office Action only maintains rejections set forth in the previous Office Action and/or sets forth new rejections that are necessitated by amendment, this Office Action is made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 67, 68 and 76-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an ET-743 concentration of up to 50nM that is "effective" to produce "minimal cytotoxic effects," does not reasonably provide enablement for any concentration that is "effective" to produce "minimal cytotoxic effects." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

invention commensurate in scope with these claims. **This is a new rejection that is necessitated by amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a method of increasing the efflux of an agent from a cell by administering an effective amount of the drug ET-743 in such an amount that does not cause cytotoxicity to the cell, yet still has an effect to cause the efflux of a drug through its up-regulation of MDR (the multi-drug resistance gene) via activation of SXR. The amount of ET-743 that is administered is necessary to practice the invention, and is in fact that most important aspect of the claimed method.

Scope of the invention. The scope of the invention is both indefinite (see rejections under 35 USC § 112, second paragraph below) and very broad. The scope is indefinite because it is unclear what amounts of ET-743 can be used to achieve the purpose of the method; that is, it is unclear what amounts can cause the efflux of an agent from a cell while not having a cytotoxic effect on the cell. Regarding the breadth of the scope, it is unclear if the amounts that are used in the claimed method reads on amounts of ET-743 that are already used in therapeutic methods.

State of the art. The prior art indicates that ET-743 is a well-known anticancer agent that. Furthermore, there are many known methods that use agents such as ET-743 to treat various diseases (see for example Martinez *et al.*, *PNAS* **96**: 3496-3501, 1999; see entire document; henceforth Martinez; and Rinehart *Med. Res. Rev.* **20**: 1-27, 2000; see entire document; henceforth Martinez). The instantly claimed method does not indicate what amounts of ET-743 are "effective" to cause efflux of an agent while causing "minimal" toxicity, or what level of toxicity is equivalent to "minimal" standards. Thus, not only can the skilled artisan not practice the claimed method for lack of an ability to administer the proper amount of ET-743, the skilled artisan cannot be apprised whether or not other methods of using ET-743 are equivalent to the instantly claimed method.

Number of working examples and Guidance provided by applicant. The instant specification indicates that amounts of ET-743 that are "effective" to cause efflux of an agent while causing only "minimal" cytotoxic effects in a cell are within the range of 0-50nM. Therefore, regarding the relative and indefinite nature of the terms "effective" and "minimal," the skilled artisan cannot ascertain how to use the method outside of the indicated range because the most important aspects of the claim (i.e., the amount of ET-743 used, and the acceptable amount of cellular toxicity) are indefinite.

Unpredictability of the art and Amount of experimentation required. The claimed invention is highly unpredictable because it is unclear what amounts of ET-743 are required to be effective in the induction of efflux of a drug from a cell while not causing significant toxicity to the cell. These amounts are vital to the practice of the claimed method, and due to the indefinite nature of the terms "effective" and "minimal," the skilled artisan cannot use the claimed invention because they cannot be certain what

amounts of the operative agent (i.e., ET-743) meet the limitations of the claims. Indeed, the invention is so unpredictable that the skilled artisan cannot even be sure if a previous method of administering ET-743, such as the one disclosed by Martinez or Rinehart, meets the limitations of the claims. Without a definitive amount or range of ET-743 that is to be used to achieve the desired result set forth in the method, the skilled artisan would be required to practice undue and unpredictable trial and error experimentation in order to practice the claimed invention.

In conclusion, the use of the terms "effective" and "minimal" in the claim language renders the claims as non-enabled. This is because the skilled artisan cannot use the method without a clear concept of what amounts of the operative agents can or must be used in the method to achieve the desired result (in this instance, the efflux of an agent from a cell without the cause of cytotoxicity).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 68, 69 and 76-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection that is necessitated by amendment.**

The term "effective" in claims 68, 69 and 78 is a relative term which renders the claim indefinite. The term "effective" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The range of ET-

743 that is effective for the claimed method is not set forth in the indicated claims, therefore the metes and bounds are not defined for what is "effective" to practice the method. As a result, the claim is indefinite.

The term "minimal cytotoxic effects" in claims 68, 69 and 78 is a relative term which renders the claim indefinite. The term "minimal cytotoxic effects" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The range of ET-743 that results in "minimal cytotoxic effects" in the claimed method is not set forth in the indicated claims, therefore the metes and bounds are not defined for what is considered "minimal cytotoxic effects." As a result, the claim is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 68-78 are rejected under 35 U.S.C. 102(b) as being anticipated by Martinez (as cited above in the rejection of 35 USC § 112, first paragraph, Enablement). **This is a new rejection that is necessitated by amendment.**

Martinez teaches the administration of ET-743 to cancer cell lines in amounts falling within the most limiting range (between 25-50nM) of the claims (74 and 75) of the instant application. For example, see the bottom panel of Figure 3, where Martinez

teaches the administration of between 10 and 100nM of ET-743. Since amounts within this range are specifically set forth in the instant claims and specification, the teachings of Martinez must necessarily fall within the range of what is "effective" with "minimal cytotoxic effects" despite the indefinite nature of those terms. Furthermore, Martinez teaches that this administration can occur in patients by disclosing that the agent ET-743 is currently undergoing phase II clinical trials (see for example, the first paragraph of the Introduction). As such, Martinez teaches each and every aspect of the claimed invention, and thus anticipates the claimed invention.

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 68-78 are rejected under 35 U.S.C. 102(a) as being anticipated by Rinehart (as cited above in the rejection of 35 USC § 112, first paragraph, Enablement). **This is a new rejection that is necessitated by amendment.**

Rinehart teaches the administration of ET-743, *in vivo* and *in vitro*, in amounts falling within the most limiting range (between 25-50nM) of the claims (74 and 75) of the instant application (see for example page 14-24). For example, see Tables XV, XV, XIX and XXII, where Rinehart teaches the administration of either 10nM (Tables XV and XVI) or the administration of 27μg/Kg (Tables XIX and XXII; note 27μg/Kg is approximately equal to a concentration of 30nM considering the weight to volume conversion of water, where 1 Kg is equivalent to 1 L, and the molecular weight of ET-743 at 760) of ET-743 *in vitro* (to cells) or *in vivo* (to a patient in need thereof). Since amounts within this range are specifically set forth in the instant claims and specification,

the teachings of Rinehart must necessarily fall within the range of what is "effective" with "minimal cytotoxic effects" despite the indefinite nature of those terms. Furthermore, Rinehart teaches that this administration can occur in patients by disclosing that the agent ET-743 is currently undergoing phase II clinical trials (see for example, the fifth full paragraph of page 14). As such, Rinehart teaches each and every aspect of the claimed invention, and thus anticipates the claimed invention.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU 1636

JAMES KETTER
PRIMARY EXAMINER